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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/590,789	MELTON ET AL.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-63* is/are pending in the application.

4a) Of the above claim(s) *20-24 and 47-61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19,25-46,62 and 63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/8/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Claims 1-63 are presented for examination.

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-19, 25-46, 62, and 63, in the reply filed on 4/21/2010 is acknowledged.

Applicant's election without traverse of i) tomudex as the antifolate compound (claim 2); ii) GARFT as the inhibited enzyme (claim 12); iii) LY309887 as the antifolate compound (claim 13); iv) AG2037 as the antifolate compound; and v) cancer as the disease (claim 43), in the reply filed on 4/21/2010 is acknowledged.

Claims 20-24 and 47-61 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention/specie(s), there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 4/21/2010.

Priority

This U.S. Non-Provisional application is a 371 of PCT/GB2005/000751, filed 2/28/2005, and claims foreign priority to GB 0404487.1, filed 2/28/2004.

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Information Disclosure Statement

Receipt is acknowledged of the Information Disclosure Statement filed 1/8/2007. The Examiner has considered the references cited therein to the extent that each is a proper citation. Please see the attached USPTO Form 1449.

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be

incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Preliminary Claim Amendments

Receipt is acknowledged of Applicants' replacement pages 45-50, filed 8/25/2006. Pursuant to the Notice of Non-Compliant Amendment mailed 5/5/2009, Applicants' Preliminary Claim Amendments were **not** entered. Accordingly, objections/rejections set forth in this Office Action are based on the originally filed claim set.

The Examiner notes that Applicants' proposed preliminary amendments to the claims did not conform to U.S. practice. Applicants are respectfully reminded that any future claim amendments must comply with 37 CFR 1.121.

Claim Rejections - 35 USC § 112 – 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-19, 25-44, and 63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 3-19, 25-44, and 63 depend from claim 2, which recites parenthetical information, e.g., "Tomudex (Formula IV)". Such parenthetical information renders the claims indefinite because there are no formulas recited in instant claim 2.

Claims 2-19, 25-44, and 63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 2, 15, and 41 contain the trade name Tomudex®. M.P.E.P. § 2173.05(u) states, "It is important to recognize that a trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus a trademark or trade name

does not identify or describe the goods associated with the trademark or trade name." If the trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. § 112, second paragraph. *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982).

Claims 5 and 7-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The metes and bounds of the limitation, "a predetermined level indicating toxicity", as recited in claim 5 are not clear.

Claims 6-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 6 recites the limitation "the predetermined blood plasma level" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

Claims 25-30, 32-35, 37-43, 45-46, and 63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 25, 37, and 45 provide for the use of an enzyme that has carboxypeptidase G activity, but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 31-35, 38-44, 46, and 63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 31 and 44 provide for the use of an antifolate compound of Formula I as defined in Claim 1 or Claim 2, but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is

intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 36, 38-44, 46 and 63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 36 provides for the use of a folate rescue agent, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass.. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 112 – 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-19, 25-46, and 62-63 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

The claims are drawn to methods comprising administering "an enzyme that has carboxypeptidase G activity". Applicants disclose one specific enzyme, carboxypeptidase G_2 (CPG_2), EC number 3.4.22.12 (page 13, lines 6-7). Enzymes having carboxypeptidase G activity, as described in the specification, can include "a derivative of CPG_2 that has carboxypeptidase activity" (page 13, lines 15-18), a "variant" of CPG2 (page 14, lines 11-16), modified CPG2 enzymes (page 16, lines 4-11), and fusions of CPG_2, or a fragment or variant thereof, to another compound (page 16, lines 13-18). Thus, the claims are drawn to a genus of enzymes that is defined only by biological activity, *i.e.*, carboxypeptidase G activity.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of the complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present is that the enzyme has carboxypeptidase G activity. There is no description of structural characteristics that are required to maintain carboxypeptidase G activity. Accordingly, in the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus of enzymes that have carboxypeptidase G activity, other than carboxypeptidase G_2 (EC number 3.4.22.12; SEQ ID:1).

Whether a few enzymes known to have carboxypeptidase G activity are known in the art is not the issue; the claims are drawn to methods comprising administering any enzyme having carboxypeptidase G activity, including those known and those yet to be identified. Applicant provides no guidance for identifying additional enzymes having carboxypeptidase G activity except for trial-and-error screening: page 13, lines 20-28; page 14, lines 6-9; and page 14, lines 11-16 of the specification. The cited claims are drawn in part to a method for combating toxicity caused by an antifolate compound of Formula I comprising administering unspecified enzymes to patients.

In University of Rochester v. G.D. Searle & Co., 68 USPQ2d 1424 (DC WNY 2003), at issue was a patent directed to method for inhibiting prostaglandin (PGHS-2) synthesis in a patient using an unspecified compound. The District Court of Western New York evaluated the level of disclosure required to satisfy the written description. In their decision (which was later affirmed by the CAFC), the District Court wrote, "The real issue here is simply whether a written description of a claimed method of treatment is adequate where a compound that is necessary to practice that method is described only in terms of its function, and where the only means provided for finding such a compound is essentially a trial-and-error process."

The patent in *Rochester* does no more than describe the desired function of the compound called for, and it contains no information by which a person of ordinary skill in the art would understand that the inventors possessed the claimed invention. At best, it simply indicates that one should run tests on a wide spectrum of compounds in the hope that at least one of them will

work. The specification of the patent in *Rochester* states that the invention comprises, *inter alia*, "assays for screening compounds, including peptides, polynucleotides, and small organic molecules to identify those that inhibit the expression or activity of the PGHS-2 gene product; and methods of treating diseases characterized by aberrant PGHS-2 activity using such compounds." Nowhere, however, does it specify which "peptides, polynucleotides, and small organic molecules" have the desired characteristic of selectively inhibiting PGHS-2.

The *Rochester* court cited the CAFC in *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316 (63 USPQ2d 1609), which adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement ("Guidelines"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including, inter alia, "functional characteristics *when coupled with a known or disclosed correlation between function and structure* ...." *Enzo*, 296 F.3d at 1324-25 (quoting Guidelines, 66 Fed. Reg. at 1106 (emphasis added)).

The *Rochester* court also cited the CAFC in *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 [43 USPQ2d 1398] (Fed. Cir. 1997), in which the court drew a distinction between genetic material and other chemicals; in drawing this distinction, however, the court also stated that "[i]n claims involving [non-genetic] chemical materials, *generic formulae usually indicate with specificity what the generic claims encompass*. One skilled in the art can distinguish such a formula from others and *can identify many of the species* that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus." 119 F.3d at 1568 (emphasis added). There is no such specificity here, nor could one skilled in the art identify any particular enzymatic effector encompassed by the claims.

The "written description" requirement may be satisfied by using such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention. See *Noelle v. Lederman*, 355 F.3d 1343, 1349, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) and *Lockwood v. American Airlines, Inc.*, 107 F.3d at 1572, 41 USPQ2d at 1966. A definition by function alone "does not suffice" to sufficiently describe a coding sequence "because it is only an indication of what the gene does, rather than what it is." *Regents of the University of California*

v. Eli Lilly & Co., 119 F.3 at 1568, 43 USPQ2d at 1406 (Fed. Cir. 1997) (discussing *Amgen Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991)). In *Fiefs v. Ravel*, 984 F.2d at 1169-71,25 USPQ2d at 1605-06 (1993), the CAFC found that "a mere wish or plan for obtaining the claimed chemical invention" is not sufficient to describe a chemical invention (discussed in *Eli Lilly* at 1404).

The fact pattern in this case is similar to that in *Rochester*. In *Rochester*, there were no compounds known to have the required function, and in the instant application, only **ONE** enzyme having carboxypeptidase G activity is disclosed. The key similarity between the cases, and the one relevant to this ground of rejection, is the fact that no method (other than trial-and-error) is provided for identifying enzymes having the desired function. For this reason, the rejection due to lack of written description is proper

Therefore, only carboxypeptidase G_2 (EC number 3.4.22.12; SEQ ID:1), but not the full breadth of the claims, meets the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that *Vas-Cath* makes it clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see *Vas-Cath* at page 1115). See also *In re Barker*, 559 F.2d 588, 591, 194 USPQ 470, 472 (CCPA 1977) (a specification may be sufficient to enable one skilled in the art to make and use the invention, but still fail to comply with the written description requirement).

Claims 1-19, 25-46, and 62-63 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reducing toxicity of raltitrexed (Tomudex®) comprising administering carboxypeptidase G_2, does not reasonably provide enablement for reducing toxicity of other compounds of Formula I comprising administering carboxypeptidase G_2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This is a Scope of Enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.

In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

The nature of the invention, and breadth of the claims

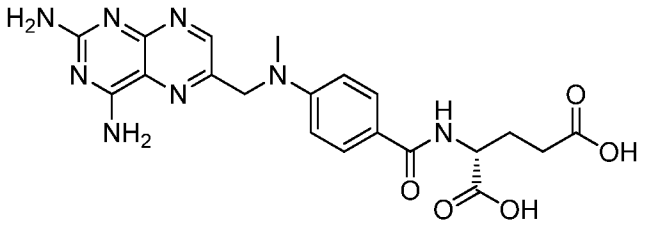
The invention is drawn to methods of combating toxicity caused by an antifolate compound of Formula I, comprising administering to an individual who has been administered said compound of Formula I an enzyme that has carboxypeptidase G activity. The claims are extremely broad in so far as the claims encompass combating toxicity of a plethora of structurally diverse compounds comprising administering "an enzyme that has carboxypeptidase G activity".

The state and predictability of the art, and relative skill of those in the art

Some compounds of Formula I as recited in the instant claims are known to inhibit enzymes involved in the folate pathway of DNA, RNA, and protein synthesis. Such compounds belong to the same class of antifolates as methotrexate. See McGuire (Current Pharmaceutical Design, 2003, vol. 9, pages 2593-2613).

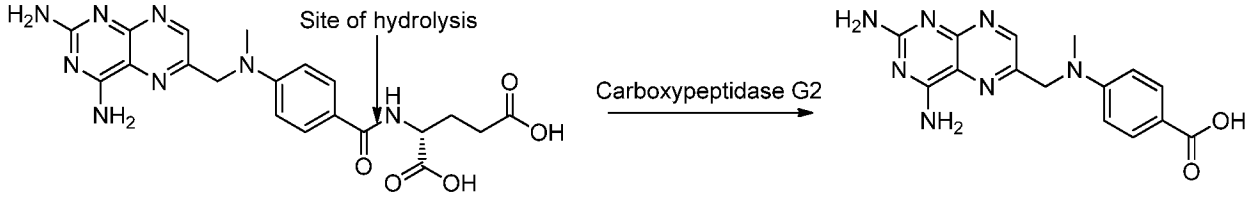
Carboxypeptidase G was known to hydrolyze the peptide bond of folate antagonists such as methotrexate, 4-amino,^{10}*N*-methylpteroylaspartic acid, aminopterin, 4-aminopteroylaspartic acid, folic acid, leucovorin, and 5-methyltetrahydrofolic acid. All of these compounds have very similar structures and all contain C-terminal glutamate residues. See Kalghatgi *et al.* (Enzymes and Drugs, J. Holcenberg and J. Roberts, eds., Wiley, New York, 1981, pages 77-102).

Methotrexate, whose structure is shown below, was known to be cleaved *in vivo* by carboxypeptidase G_1 and G_2. See, *inter alia*, **Adamson *et al***. (Journal of Clinical Oncology, 1991, vol. 9, no. 4, pages 670-674); **Kalghatgi *et al***. (Enzymes and Drugs, J. Holcenberg and J. Roberts, eds., Wiley, New York, 1981, pages 77-102); and **Widermann *et al***. (Proceedings of ASCO, 1998, vol. 17, Abstract 855).



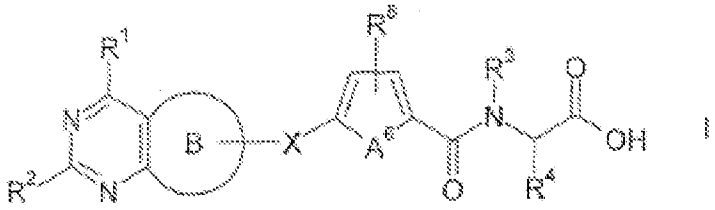
Methotrexate

Carboxypeptidase G_2 catalyzes the hydrolysis of the C-terminal glutamate residue from methotrexate.

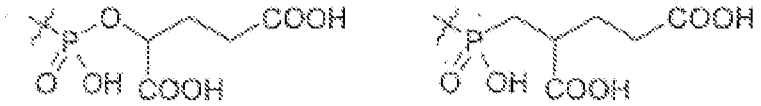


Methotrexate

The claimed compounds of Formula I encompass a plethora of structurally diverse compounds as shown below.



R4 is defined in the instant claims to encompass $-CH_2C(R^{9a})(R^{9b})$-D, wherein D represents C(O)OH, tetrazol-5-yl, $(CH_2)_{0-1}$-NHR^{11}, or, when R^{9a} and R^{9b} together represent $=C(H)R^{10}$, then D may also represent H, or D represents a structural fragment of Formula IIIa or IIIb,



IIIa IIIb

Note that only when R^{9a} and R^{9b} are H and D is C(O)OH does a compound of Formula I contain a glutamate group known to be cleaved by carboxypeptidase G_2.

Raltitrexed (Tomudex) was also known in the prior art to also be hydrolyzed in the same position as methotrexate. See Bisset *et al.* (J. Med. Chem., 1992, vol. 35, pages 859-866) at page 862, Scheme II.

The prior art thus teaches that carboxypeptidase G specifically hydrolyzes the peptide bond of antifolate antagonists containing a C-terminal glutamate. The prior art does not teach or suggest that carboxypeptidase G is capable of hydrolyzing other C-terminal groups such as those broadly encompassed by the instant claims.

As a general rule, enablement must be commensurate with the scope of claim language. MPEP 2164.08 states, "The Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to **make and use the full scope of the claimed invention** without undue experimentation'." *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)" (emphasis added). The "make and use the full scope of the invention without undue experimentation" language was repeated in 2005 in *Warner-Lambert Co. v. Teva Pharmaceuticals USA Inc.*, 75 USPQ2d 1865, and *Scripps Research Institute v. Nemerson*, 78 USPQ2d 1019 asserts: "A lack of enablement for the full scope of a claim, however, is a legitimate rejection." The principle was explicitly affirmed most recently in *Auto. Tech. Int'l, Inc. v. BMW of N. Am., Inc.*, 501 F.3d 1274, 84 USPQ2d 1108 (Fed. Cir. 2007), *Monsanto Co. v. Syngenta Seeds, Inc.*, 503 F.3d 1352, 84 U.S.P.Q.2d 1705 (Fed. Cir. 2007), and *Sitrick v. Dreamworks, LLC*, 516 F.3d 993, 85 USPQ2d 1826 (Fed. Cir. 2008). See also *In re Cortright*, 49 USPQ2d 1464, 1466 and *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer Inc.*, 49 USPQ2d 1370.

By way of background, four cases are of particular relevant to the question of enablement of a methods encompassing broad genera where limited working examples are provided:

In *In re Buting*, 57 CCPA 777, 418 F.2d 540, 163 USPQ 689, the claim was drawn to "The method of treating a malignant condition selected from the group consisting of leukemias, sarcomas, adenocarcinomas, lymphosarcomas, melanomas, myelomas, and ascitic tumors" using a small genus of compounds. The Court decided that human testing "limited to one compound and two types of cancer" was not "commensurate with the broad scope of utility asserted and claimed".

In *Ex parte Jovanovics*, 211 USPQ 907 the claims were drawn to "the treatment of certain specified cancers in humans" by the use of a genus of exactly two compounds, the N-formyl or N-desmethyl derivative of leurosine. Applicants submitted "affidavits, publications and data" for one of the compounds, and a dependent claim drawn to the use of that species was allowed. For the other, no data was presented, applicants said only that the other derivative would be expected to be less effective; claims to the genus were refused.

In *Ex parte Busse*, et al., 1 USPQ2d 1908, claims were drawn to "A therapeutic method for reducing metastasis and neoplastic growth in a mammal" using a single species. The decision

notes that such utility "is no longer considered to be "incredible", but that "the utility in question is sufficiently unusual to justify the examiner's requirement for substantiating evidence. Note also that there is also a dependent claim 5 which specified "wherein metastasis and neoplastic growth is adenocarcinoma, squamous cell carcinoma, melanoma, cell small lung or glioma." The decision notes that "even within the specific group recited in claim 5 some of the individual terms used actually encompass a relatively broad class of specific types of cancer, which specific types are known to respond quite differently to various modes of therapy."

In *Ex parte Stevens*, 16 USPQ2d 1379 a claim to "A method for therapeutic or prophylactic treatment of cancer in mammalian hosts" was refused because there was "no actual evidence of the effectiveness of the claimed composition and process in achieving that utility."

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. That factor is outweighed, however, by the unpredictable nature of the art.

It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved" and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ 2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain). As long as the Specification discloses at least one method of making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112, 1st Paragraph is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). To that extent, if little is known in the prior art about the nature of the invention and the art is unpredictable, the Specification would need more detail as to how to make and use the invention in order to be enabling. See *Chiron Corp v. Genetech, Inc.*, 363 F.3d 1247, 1254, 70

USPQ2d 1321, 1326 (Fed. Cir. 2004) ("Nascent technology, however, must be enabled with a specific and useful teaching. The law requires an enabling disclosure for nascent technology because a person of ordinary skill in the art has little or no knowledge independent from the patentee's instruction. Thus, the public's end of the bargain struck by the patent system is a full enabling disclosure of the claimed technology.")

The amount of direction or guidance provided and the presence or absence of working examples

The specification is purely hypothetical in so far as there are no working examples demonstrating a reduction in toxicity of a compound of Formula I in a subject by administration of an enzyme having carboxypeptidase G activity. While Applicants describe methods of rescue of Tomudex toxicity by CPG_2 (Examples 2 and 3), these examples appear to be descriptive only, i.e., no results are provided.

Applicants provide evidence that Tomudex is a substrate for carboxypeptidase G_2 *in vitro* and that carboxypeptidase G_2 deglutamates tomudex *in vitro* (Example 1A). No other compounds of Formula I, particularly compounds of Formula I that do not contain C-terminal glutamate, have been shown by Applicants to be hydrolyzed by any enzyme having carboxypeptidase G activity.

The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that enzymes having carboxypeptidase G activity could be predictably used to combat toxicity of antifolate compounds of Formula I as inferred in the claims and contemplated by the specification.

Genentech Inc. vs. Nova Nordisk states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).

In the instant case, Applicants have presented a general idea that because Tomudex is a substrate for carboxypeptidase G_2 then "an enzyme that has carboxypeptidase G activity" must therefore, *a priori*, be useful in combating toxicity of antifolate compounds of Formula I. However, the claims encompass a multitude of compounds (perhaps millions) having a plethora of chemically and biologically distinct substituents. Applicants demonstrated that Tomudex, an antifolate similar in structure to methotrexate and containing a C-terminal glutamate, is hydrolyzed *in vitro* by carboxypeptidase G_2. No other compounds of Formula I have been demonstrated by Applicants to be substrates for carboxypeptidase G_2. Applicants have presented no factual evidence that carboxypeptidase G_2 is capable of hydrolyzing compounds of Formula I that do not contain a C-terminal glutamate group as found in all antifolate compounds known in the art to be hydrolyzed by carboxypeptidase G.

Determining if the toxicity of any particular claimed compound could be combated by administration of "an enzyme that has carboxypeptidase G activity" would require synthesis of the compound, formulation into a suitable dosage form, administration of the compound of Formula I, determining toxicity of the administered compound of Formula I, administering an enzyme that has carboxypeptidase G activity, and measuring reduction in toxicity elicited by administration of the enzyme. This is undue experimentation given the limited guidance and direction provided by Applicants.

Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 25-46 and 62-63 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See

for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 25-36, 38-46, and 62-63 are rejected under 35 U.S.C. 102(b) as being anticipated by **DeAngelis *et al.*** (J. Clin. Oncol., 1996, vol. 14, pages 2145-2149).

DeAngelis *et al.* studied the safety and efficacy of carboxypeptidase G_2 (CPG_2) rescue for high-dose MTX in patients with recurrent cerebral lymphoma (Abstract). Four patients with recurrent primary CNS lymphoma received 3.0 mg/m^2 MTX infused over 2 hours and twelve hours after the start of MTX, 50 U/kg CPG_2 was infused and a second dose of CPG_2 was given 6 hours after the first (Abstract; pages 2145-2146, "Patients and Methods"). All patients had a rapid and prominent decrease in plasma MTX concentration within 5 minutes of CPG_2 administration (paragraph bridging pages 2146 and 2147; Figure 1). The authors conclude that, unlike leucovorin, CPG_2 rescues organs by terminating their exposure to MTX (paragraph bridging pages 2147 and 2148). The treated patients had no evidence of MTX toxicity with CPG_2 rescue (page 2148, left column).

The authors thus teach use of an enzyme that has carboxypeptidase G activity in the preparation of a medicament. Applicants' recitation of an intended use, *i.e.*, "for combating toxicity caused by an antifolate compound of Formula I as defined in Claim 1 or Claim 2", does not distinguish the medicament of the instant claims from that taught in DeAngelis *et al.*

Claims 25-46 and 62-63 are rejected under 35 U.S.C. 102(b) as being anticipated by **Widemann *et al***. (J. Clin. Oncol., 1997, vol. 15, no. 5, pages 2125-2134) (newly cited) (Abstract attached).

Widemann *et al*. teach that $CPDG_2$ rapidly hydrolyzes methotrexate to inactive metabolites. Widemann *et al*. teach administration of one to three doses $CPDG_2$ (50 U/kg), thymidine (8 g/m^2), and leucovorin to patients with high-dose methotrexate-induced renal dysfunction (Abstract).

The authors thus teach use of an enzyme that has carboxypeptidase G activity and a folate pathway rescue agent in the preparation of a medicament. Applicants' recitation of an intended use, *i.e*., "for combating toxicity caused by an antifolate compound of Formula I as defined in Claim 1 or Claim 2", does not distinguish the medicament of the instant claims from that taught in Widemann *et al*.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-10, 19, 25-36, 40-46, and 62-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Adamson *et al.*** (J. Clin. Oncol., 1991, vol. 9, pages 670-674), **Adamson *et al.*** (J. Clin. Oncol., 1992, vol. 10, pages 1359-1364), **DeAngelis *et al.*** (J. Clin. Oncol., 1996, vol. 14, pages 2145-2149), and **Krause *et al.*** (Leukemia and Lymphoma, 2002, vol. 43, no. 11, pages 2139-2143) in view of **Clarke *et al.*** (Clin. Pharmacokinetics, 2000, vol. 39, no. 5, pages 429-443), **Kalghatgi *et al.*** (Enzymes and Drugs, J. Holcenberg and J. Roberts, eds., Wiley, New York, 1981, pages 77-102), and **Bisset *et al.*** (J. Med. Chem., 1992, vol. 35, pages 859-866) (newly cited).

Claimed Invention

The instant claims recite methods of combating toxicity caused by an antifolate compound of Formula I in an individual who has been administered said compound, comprising administering to the individual an enzyme that has carboxypeptidase G activity.

Teachings of Adamson et al. (1991)

Adamson *et al.* teach that the carboxypeptidase G class of enzymes rapidly hydrolyze methotrexate (MTX) into the inactive metabolites 4-deoxy-4-amino-N^{10}-methylpteroic acid (DAMPA) and glutamate (Abstract). The instant study of Adamson *et al.* evaluated the use of carboxypeptidase G_2 ($CPDG_2$) as a potential intrathecal rescue agent for massive MTX overdose (*id.*).

Groups of monkeys received (1) MTX alone (5 mg), (2) MTX (5 mg) followed 5 minutes later by $CPDG_2$ (30 U), or (3) $CPDG_2$ (30 U) alone (page 671, left column, "Pharmacokinetics of $CPDG_2$ Rescue"). As shown in Figure 1, administration of $CPDG_2$ resulted in a greater than 400-fold decrease in MTX concentrations (page 671, right column).

Carboxypeptidase G enzymes such as $CPDG_1$ and $CPDG_2$ have been administered systemically to patients as rescue therapy following high-dose MTX and also have been used to detoxify patients with renal failure following MTX dosing (page 672, right column).

The authors conclude that $CPDG_2$ may prove to be an important addition to the currently recommended strategy for the management of MTX overdose (page 673, right column).

Teachings of Adamson et al. (1992)

Similar to Adamson *et al.* (1991), Adamson *et al.* (1992) teaches that $CPDG_2$ rapidly hydrolyzes MTX to inactive metabolites and has more potential advantages than standard leucovorin rescue (Abstract). The authors studied the effects of $CPDG_2$ administration to monkeys administered 300 mg/m^2 MTX loading dose followed by a 60 mg/m^2/hour infusion of MTX during an 18 hour period (*id.*). 0.5 mL $CPDG_2$ (50 U/kg) was administered by IV on completion of the MTX infusion (page 1360, right column). As shown in Figure 2, $CPDG_2$ dramatically decreased plasma MTX concentrations to "nontoxic levels" (Abstract; Figure 2).

Teachings of DeAngelis et al.

DeAngelis et al. studied the safety and efficacy of carboxypeptidase G_2 (CPG_2) rescue for high-dose MTX in patients with recurrent cerebral lymphoma (Abstract). Four patients with recurrent primary CNS lymphoma received 3.0 mg/m^2 MTX infused over 2 hours and twelve hours after the start of MTX, 50 U/kg CPG_2 was infused and a second dose of CPG_2 was given 6 hours after the first (Abstract; pages 2145-2146, "Patients and Methods"). All patients had a rapid and prominent decrease in plasma MTX concentration within 5 minutes of CPG_2 administration (paragraph bridging pages 2146 and 2147; Figure 1). The authors conclude that, unlike leucovorin, CPG_2 rescues organs by terminating their exposure to MTX (paragraph bridging pages 2147 and 2148). The treated patients had no evidence of MTX toxicity with CPG_2 rescue (page 2148, left column).

Teachings of Krause et al.

Krause *et al.* teach that high-dose methotrexate (MTX) is a component of many cancer treatment regimens but that, despite careful management, delayed renal clearance followed by extremely high serum levels with potentially life-threatening toxicity can occur. In the present study, the authors evaluated carboxypeptidase G_2 ($CPDG_2$) rescue in 8 patients with delayed methotrexate elimination and renal impairment after high-dose MTX therapy for lymphoma and osteosarcoma (Abstract).

Patients were treated with six cycles of chemotherapy containing combinations of methotrexate (5 g/m^2 over 24 hours) and other chemotherapeutic agents. Carboxypeptidase G_2

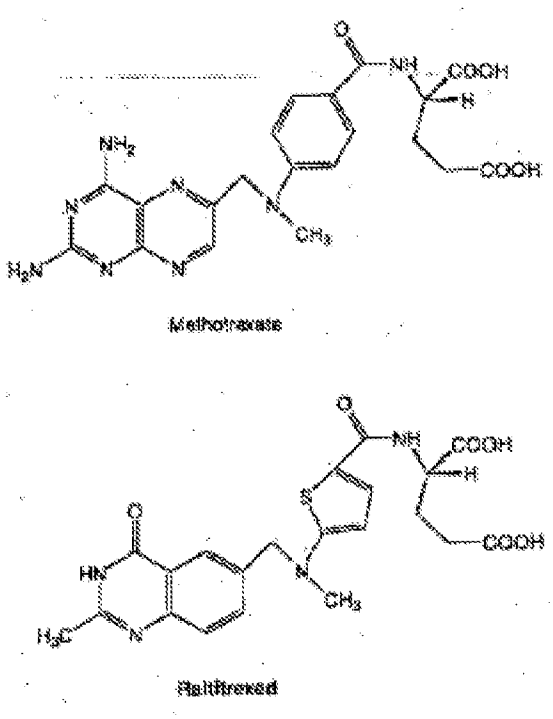
was administered in a dose of 50 U/kg over 5 minutes (page 2140, right column). As shown in Figure 1, $CPDG_2$ administration dramatically lowered MTX plasma concentration in the treated patients.

The authors conclude that $CPDG_2$ is highly effective in preventing life-threatening toxicity in patients with MTX induced renal failure and delayed drug clearance and is safe and well tolerated (page 2143, left column).

Teachings of Clarke et al.

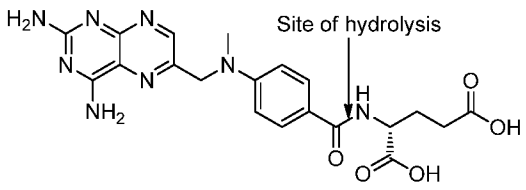
Clarke et al. teach that raltitrexed is a specific, folate-based inhibitor of thymidylate synthase with activity in advanced colorectal cancer (page 429). Apart from polyglutamation, raltitrexed does not appear to be metabolized to a significant extent and most of the excreted drug is recovered unchanged in the urine within the first 24 hours post-administration (page 430). While the average clearance of raltitrexed in 2.4 L/h (40 mL/min.), this value is significantly reduced in patients with compromised renal function and these patients are more likely to experience severe antiproliferative toxicity with raltitrexed (*id.*). In this regard, a study in cancer patients with renal impairment administered 3 mg/m2 raltitrexed every 3 weeks demonstrated that while there were no significant differences in mean C_{max} between patients with renal impairment and those without, the mean AUC was significantly higher in patients with renal impairment and treatment-related toxicities were significantly greater in patients with renal impairment (pages 437-438).

Figure 1 of Clarke *et al.* shows the structural similarity of ralititrexed to methotrexate.

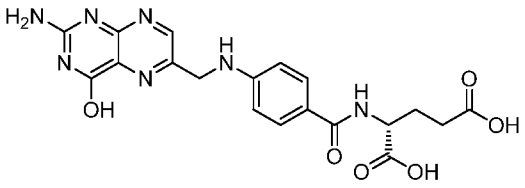


Teachings of Kalghatgi et al.

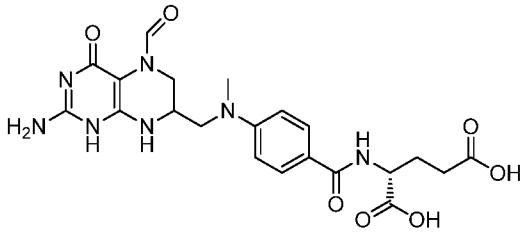
Kalghatgi *et al*. carboxypeptidase G enzymes hydrolyze the peptide bond of folate antagonists (page 82; page 83, Figure 3). Regarding substrate specificity of carboxypeptidase G enzymes, the authors teach that the enzymes from different sources exhibit considerable variation in substrate specificity, however all carboxypeptidase G enzymes hydrolyze folate derivatives with glutamic acid at the C-terminal (page 86). Table 2 demonstrates that carboxypeptidase G enzymes hydrolyze the C-terminal glutamate from methotrexate, 4-amino,^{10}*N*-methylpteroylaspartic acid, aminopterin, 4-aminopteroylaspartic acid, folic acid, leucovorin, and 5-methyltetrahydrofolic acid.



Methotrexate



Folic Acid



Leucovorin

Teachings of Bisset et al.

Bisset *et al.* is provided as evidence that raltitrexed is a substrate for carboxypeptidase G_2. In this regard, the authors demonstrate that raltitrexed is hydrolyzed by carboxypeptidase G_2 in the same position as methotrexate (Scheme II; page 863, left column). In Scheme II of Bisett *et al.*, compound **8** is raltitrexed, a compound of the instantly claimed Formula I when R^1 is OH, R^2 is methyl, B is Formula Ia (wherein A^1 and A^2 are CH and R^{5a} is hydrogen), X is $-CH_2NR^{7b}$ (wherein R^{7b} is methyl), A^6 is S, R^8 is hydrogen, R^3 is hydrogen, and R^4 is $-CH_2C(R^{9a})(R^{9b})$-D (wherein R^{9a} and R^{9b} are H and D is C(O)OH).

Examiner's Determination of Obviousness

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer carboxypeptidase G_2 to combat toxicity associated with the administration of raltitrexed. The skilled artisan would have been motivated to do so because carboxypeptidase G_2 was known in the art to effective in reducing the toxicity of the related antifolate compound, methotrexate, via hydrolyses of the C-terminal glutamate of methotrexate. As evidenced by Bisset *et al.*, raltitrexed is also a substrate for carboxypeptidase G_2, wherein the C-terminal glutamate of raltitrexed is also hydrolyzed by the enzyme. As such, the skilled artisan would expect that administration of carboxypeptidase G_2 to patients undergoing treatment

with raltitrexed would result in lowering of raltitrexed plasma concentrations and reduction in toxicity, just as is seen in patients administered carboxypeptidase G_2 who are undergoing treatment with methotrexate.

Applicants predicate patentably of their invention in part on the fact that raltitrexed is a substrate for carboxypeptidase G_2. Applicants state that it was not known whether any folate compounds other than folic acid, MTX, 5-methyl THF, and 5-formyl THF were substrates for CPG_2 and it was not known, and could not be predicted, whether any of the new generation of antifolate drugs are substrates for CPG_2 cleavage (page 7, lines 12-15). However, as evidenced by Bisset *et al.*, this is not the case. It was known prior to Applicants' invention that raltitrexed was a substrate for CPG_2 and is hydrolyzed by CPG_2. As such, Applicants' demonstration that CPG_2 cleaves raltitrexed is not a patentable contribution to the art.

Claims 11-18 and 37-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Adamson *et al.*** (J. Clin. Oncol., 1991, vol. 9, pages 670-674), **Adamson *et al.*** (J. Clin. Oncol., 1992, vol. 10, pages 1359-1364), **DeAngelis *et al.*** (J. Clin. Oncol., 1996, vol. 14, pages 2145-2149), and **Krause *et al.*** (Leukemia and Lymphoma, 2002, vol. 43, no. 11, pages 2139-2143) in view of **Clarke *et al.*** (Clin. Pharmacokinetics, 2000, vol. 39, no. 5, pages 429-443), **Kalghatgi *et al.*** (Enzymes and Drugs, J. Holcenberg and J. Roberts, eds., Wiley, New York, 1981, pages 77-102), and **Bisset *et al.*** (J. Med. Chem., 1992, vol. 35, pages 859-866) (newly cited) as applied to claims 1-10, 19, 25-36, 40-46, and 62-63 above, and further in view of **Widemann *et al.*** (J. Clin. Oncol., 1997, vol. 15, no. 5, pages 2125-2134) (newly cited) (Abstract attached).

Adamson *et al.* (1991), Adamson *et al.* (1992), DeAngelis *et al.*, Krause *et al.*, Clarke *et al.*, Kalghatgi *et al.*, and Bisset *et al.* teach as applied *supra* and are herein applied in their entirety for the same teachings. Claims 10-18 and 37-39 differ from Adamson *et al.* (1991), Adamson *et al.* (1992), DeAngelis *et al.*, Krause *et al.*, Clarke *et al.*, Kalghatgi *et al.*, and Bisset *et al.* in that the references do not teach a folate pathway rescue agent such as leucovorin.

Teachings of Widemann et al.

Widemann *et al*. teach that $CPDG_2$ rapidly hydrolyzes methotrexate to inactive metabolites. Widemann *et al*. teach administration of one to three doses $CPDG_2$ (50 U/kg), thymidine (8 g/m2), and leucovorin to patients with high-dose methotrexate-induced renal dysfunction (Abstract).

Examiner's Determination of Obviousness

It would have been *prima facie* obvious to administer carboxypeptidase G_2 in combination with leucovorin to reduce toxicity associated with administration of raltitrexed for the reasons discussed supra, in view of the teachings of Widemann *et al*., who teach co-administration of $CPDG_2$ and leucovorin rescues patients with high-dose MTX nephrotoxicity. As such, the skilled artisan would expect that $CPDG_2$ and leucovorin would also be effective to reduce toxicities associated with raltitrexed therapy given the fact that raltitrexed was known to also be a substrate of $CPDG_2$ as taught in Bisset *et al*.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Primary Examiner, Art Unit 1614

June 28, 2010